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PRINCIPAL INVESTIGATOR: Abbey B. Berenson, M.D.

CONTRACTING ORGANIZATION: University of Texas Medical Branch
Galveston, Texas 77555-0136

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Abbey B. Berenson, M.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Texas Medical Branch
Galveston, Texas 77555-0136

E-mail: abberens@utmb.edu

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13. ABSTRACT *(Maximum 200 Words)*

This prospective, longitudinal study examined contraceptive outcomes among active-duty military and civilian women who receive one of three different methods of contraception (Depo-Provera, Ortho-Novum 1/35 and Ortho-Cept). Outcomes examined included method continuation, satisfaction, dysmenorrhea, menstrual bleeding, pregnancy rates, bone density and plasma lipids. This final summary report details the specific activities that have occurred during Year 5 (September 23, 2000 to September 22, 2001). All major objectives were completed during year five. Twenty four month visits have been completed on all subjects. Data analysis has been completed. One paper has been published in the prestigious Ob/Gyn journal, Obstetrics & Gynecology, and two others are in preparation as this project comes to a close.

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Introduction

Operation Desert Shield/Storm involved the largest network of female soldiers from the United States ever deployed to a combat situation (1–3). Utilization data collected in one evacuation hospital found that 25% of all patient visits during the period of deployment were made by servicewomen, despite the fact that only 8% of the entire deployed force was female (2). Over 50% of all visits made by women were for gynecologic concerns as contraception, dysmenorrhea, and pelvic pain (3). In fact, 56% of medical evacuations by women were due to pregnancy (2). Relative to treatment, the continuation of or restarting of oral contraceptive pills and related bleeding disorders represented the largest number of gynecological complaints treated by this facility (3). These data demonstrate the critical need to determine the safest, most convenient, and most effective contraceptive method for women serving in the Armed Forces.

Two alternative forms of contraception which may be appropriate for use by servicewomen have recently been approved for use in the United States. In the past, most servicewomen requesting contraception have been prescribed a monophasic norethindrone-containing birth control pill (NOCA). In 1992, injectable depot medroxyprogesterone acetate (DMPA) received approval and more recently, birth control pills using the new progestin, desogestrel (DOCA), have been made available in the United States (12-14). As described below, these new formulations, when compared with the pill traditionally prescribed for servicewomen, may increase contraceptive efficacy and long-term continuation rates, as well as minimize dysmenorrhea and menstrual bleeding irregularities.

DMPA is an injectable progestational agent that offers a highly effective, safe, convenient, reversible and almost user-independent method of birth control (12). After a deep gluteal or deltoid injection of 150 mg, contraceptive plasma levels are reached within 24 hours, and peak plasma concentrations of 15-25 micrograms/ml are achieved within 20 days (12). Microcrystals are suspended in an aqueous solution that results in delayed absorption from the injection site and consequently prolongs the circulating concentration

of the active progestin (12). Thus, effective plasma concentration for this birth control method is sustained for at least 14 weeks, and ovulation is suppressed, on the average, for 18 weeks (12).

DOCA is a highly selective gonane progestin that has been approved for use in the United States in a monophasic formulation containing 150 micrograms of desogestrel and 30 micrograms of ethinyl estradiol (13,14). Desogestrel was one of the three new progestational agents synthesized from levonorgestrel that were developed and brought into clinical trials during the late 1970s (13). Although new to the U.S. market, DOCA has been used for almost a decade and is the most widely prescribed oral contraceptive pill in Europe. The available literature on this new formulation demonstrates that this new preparation is effective and well tolerated by most women (13,14).

Although each of these new methods of contraception may have unique contraceptive and health benefits for servicewomen, data comparing outcomes are not available. To achieve the specific aim set forth in this proposal, we will compare these contraceptives on selected outcomes (method continuation, satisfaction, dysmenorrhea, menstrual bleeding, pregnancy prevention, bone density, and plasma lipid levels) believed to be most critical for women serving in the Armed Forces.

Contraceptive Continuation. Although the continuation rate of pill use is reported in contraceptive textbooks to be 75% after 12 months of use (7,15), this figure is misleading. Most likely, this rate is inflated because it is based on the responses of married women whose contraceptive practices may be more consistent than a more diverse group of sexually active women (16,17). A more accurate estimate of pill continuation rates may be obtained by reviewing data from clinical trials that sample a more representative pool of women. Data from DOCA trials demonstrate that approximately 65% and 50% of women continued use of these pills for 12 and 24 months, respectively (18,19). Furthermore, these studies and others note that intermenstrual bleeding (breakthrough bleeding and spotting) is a common reason for pill discontinuation (13,14,18,19). Because decreased rates of intermenstrual bleeding have been reported with use of DOCA, higher rates of contraceptive continuation are believed to occur with this method as compared to more traditional birth control pills (13,14). Clinical trials conducted with DMPA suggest that

continuation rates with this method are even higher (80% at 12 months and 68% at 24 months) than those observed with the traditional or newer forms of oral contraceptives, perhaps because it is easy to use or because it induces amenorrhea (12,20-26). To date, however, no study has directly compared continuation rates among these different methods of contraception. The present proposal will help fill this void by systematically examining rates of continuation among three different methods of hormonal contraception after 6-, 12-, and 24-months of use.

Method Satisfaction. Factors which may influence user satisfaction and lead to contraceptive discontinuation include menstrual irregularities, weight gain, nausea, headaches, mood changes, dizziness, acne, fatigue, and breast swelling or tenderness (7,27,28). Generally, discontinuation rates due to side-effects other than menstrual irregularities are less than 4%, but can vary according to method (27,29,30). One medical side effect of particular concern to many women is weight gain. Continuous weight gain has been associated with the progestin component of hormonal contraceptives (31). Double-blinded studies among different pill formulations suggest there is little evidence that oral contraceptive use leads to increased weight (29,30). In contrast, DMPA use results in an average gain of 2-3 lb. per year (31). This side effect may be of particular concern to women serving in or planning to serve in the military, as those who gain weight secondary to contraceptive use may not meet the required weight/height physical standards unique to their branch of the armed forces after long term use. Although consistent exercise may help control this weight gain, a willingness to exercise may be impeded by DMPA use as preliminary studies suggest that this method results in increased fatigue (32).

Other issues that affect satisfaction relate to symptom improvement as a result of a particular hormonal method. For example, DOCA usually improves acne skin conditions among users. In one study of DOCA users, a significant proportion of women with acne reported complete resolution of this problem (13,14,19). Another benefit of oral contraceptives, especially DOCA, is the effect on hirsutism (13,14,19). Several studies employing this newly available oral contraceptive have reported significant improvement of this condition after 6 months of continued use. Unfortunately it is difficult to interpret data on method

satisfaction from prior contraceptive studies because increased satisfaction with a method is usually inferred from a lack of reported medical side-effects by subjects, rather than by use of specific questions to inquire about satisfaction. For example, most women who participated in the multicenter clinical trials on DOCA reported excellent cycle control, reduced intermenstrual bleeding and spotting, and among women with dysmenorrhea, reduced symptomatology (13,19) Moreover, at 6-, 12-, and 24-months of use, about 88%, 92%, and 94%, respectively, of the sample did not report any medical side-effects (19). Thus, researchers concluded that a high degree of method satisfaction, and therefore continuation, existed for those women taking this newly formulated pill (13,14,19). Investigators of DMPA found that about 64% of women did not report any medical side-effects (and thus were satisfied) in any one year during a five-year follow-up evaluation (23). Unfortunately, variations in study methodology have made it difficult to compare user satisfaction across studies and no single study has compared method satisfaction across different methods of contraception. This study will help fill this void by systematically evaluating method satisfaction including medical side-effects after 6-, 12-, and 24-months of use.

Dysmenorrhea. One of the single, largest causes of periodic absenteeism and decreased work productivity among young civilian women is dysmenorrhea (5-10). Pain with menstruation, or dysmenorrhea, represents a common gynecological complaint affecting approximately 70% of young women (5-10). Fifteen percent of young adult women who report pain with menstruation state that it is severe enough to limit usual activity even when analgesics are used (6). This disorder is commonly treated with combined oral contraceptive pills. However, 30% of women given traditionally formulated pills continued to experience moderate to severe dysmenorrhea (9). Studies of DOCA suggest that this new formulation may be more beneficial than traditional pills in ameliorating dysmenorrhea, perhaps due to a decrease in breakthrough bleeding episodes (19). For example, an open cross-over study on women with primary dysmenorrhea which did not respond to traditional pills noted that a significant number who used DOCA for 3 months reported reduced pain and 80% of the sample wished to remain on this pill

formulation (10). Another study found that 50% of women taking DOCA reported significant improvements in their dysmenorrhea after using this formulation of one month (19).

Traditionally, the therapy for dysmenorrhea has been the oral contraceptive pill because it reduces the prostaglandin content of menstrual fluid and therefore decreases uterine motility (5-10). However, specific comparative studies examining treatment efficacy of various contraceptive regimens have not been conducted. Although the etiology of dysmenorrhea has yet to be clearly elucidated, it is suspected that the amelioration of dysmenorrheic symptoms is due to the suppression of ovulation (9). Data collected from clinical DMPA trials has found that up to 70% of users are amenorrheic after 4 or more injections. Thus, if cessation of ovulation results in decreased symptoms, long-term use of DMPA may provide greater benefit than any pill formulation.

Menstrual Bleeding. All hormonal contraceptive methods affect the menstrual cycle and may influence the pattern and amount of bleeding (33). Contraceptives generally affect the menstrual cycle in one of 2 ways: (1) cyclic bleeding continues, as with oral contraceptive pills, where the hormonal formulation substitutes an artificial cycle for the woman's own cycle, but withdrawal bleeding occurs during the last 5-7 days; or (2) the normal cycle is partially or completely suppressed and the method does not induce cyclic bleeding, as with DMPA (33).

Irregular bleeding may also occur with use of hormonal contraception. However, the frequency of intermenstrual bleeding tends to decrease with continued use. Unfortunately, many clinical trials, especially those conducted 5 or more years ago, do not report their bleeding rates in a standard fashion, i.e., across 90-day reference periods (number of bleeding, spotting, and nonbleeding episodes that are summed across a 90-day period). Thus, data cannot be directly compared between formulations. Nonetheless, data collected on clinical trials of DOCA suggest a marked reduction in breakthrough bleeding (BTB) and spotting (14). Although BTB is more prevalent in the first few cycles of use (1.2-10%), by the sixth cycle, reported rates have decreased to 0.4-9.2% among users (14). With regard to spotting, rates are reported to decrease from 18.2% at cycle 1 to 5.8% by cycle 6 (14). In contrast, DMPA users commonly report episodes of

unpredictable spotting and bleeding lasting seven or more days during the first few months of use. Data collected from an efficacy study found that the average number of bleeding or spotting days per 90-day reference period was 24.2 at 3 months, 18.5 at 6 months, 10.7 at 12 months, 7.6 at 18 months, and only 6.8 days at 24 months (26). However, as women continue with this hormonal method, amenorrhea becomes common. More than 70% of women develop this condition after 4 or more injections (12). This may be of particular benefit during periods of deployment. This study will directly compare the number of bleeding days associated with use of three different hormonal methods.

Pregnancy Prevention. Unplanned pregnancy among military servicewomen accounts for a significant number of hospital visits and loss of work productivity. As previously stated, pregnancy was the single largest cause of medical evacuation out of the theater during Operation Desert Shield/Storm (3). A longitudinal investigation of Navy women who enlisted between 1973 and 1987 found that for the first year of active-duty, the highest rates of hospitalization for the 1973-77 cohort was for induced abortion, while complications of pregnancy represented the highest hospitalization rate for the 1983-87 cohort (34). Moreover, pregnancy-related conditions continued to contribute to high levels of hospitalization for the remainder of this five-year active-duty interval. With the increase of female soldiers in combat areas, it will also be critical to protect personnel who are taken prisoner from becoming pregnant as a result of rape as recent conflicts demonstrate that this act is increasing as a crime of war (35).

Used consistently and correctly, the monophasic norethindrone oral contraceptive has a theoretical efficacy rate of 99% (27). However, the actual occurrence of pregnancy is as high as 8% due to poor daily compliance (36). Contraceptive management to ensure daily adherence is challenging because noncompliance may not be a willful, conscious act. More frequently, it is due to forgetfulness or misunderstanding of when to initiate pill use or what to do when a pill is missed (27,28). In contrast, DMPA is almost user-independent. A recent cost-benefit analysis conducted for pregnancy prevention compared DMPA with two different birth control pills and Norplant® (37). These researchers reported that

among pill users, the actual contraceptive efficacy was 95% versus 99.7% among DMPA users and concluded that DMPA delivered the highest net benefit for pregnancy prevention.

Bone Density The evaluation of hormonal effects on bone density are critical to the military, because a high incidence of musculoskeletal injuries, including stress fractures, have been reported among females in the eight weeks of basic training (38), and similar problems are likely to occur in combat situations. One particular concern with the use of DMPA by military women, therefore, is the suggestion that it may adversely affect bone density. A recent study examining bone density changes in women who had used DMPA for 5 or more years found reduced lumbar spine and femoral neck densities, compared to findings in premenopausal controls (39). However, these data are somewhat difficult to interpret because the study sample was considerably older (most in their mid-40s), and over half were smokers, factors that have been shown to contribute to loss in bone density.

In contrast, three cross-sectional studies and one longitudinal study have shown that NOCA favorably affects bone mass (40-42). For example, Lindsay et al (40) examined two groups of women aged 25 to 33 years who had variable health histories and found a 1% gain in bone density occurred for each year of pill use. DOCA has been associated with maintenance of bone mass in two separate studies (14,43). Ricci, Mango, Manna, et al. (43), examined the effects on bone mass density among 17 nulliparous women who had never taken oral contraceptives. These researchers found that bone density after one year of use was comparable to pretreatment levels. Another study employing a slightly different formulation (20 micrograms of ethinyl estradiol) conducted in Italy examined premenopausal women and reported a preservation of bone mass after two years of use (44). These authors conclude that DOCA does not appear to have any deleterious effects on bone density, but does not offer any protective effects for fracture rates either. Thus, it appears that no harmful effects on bone density result from oral contraceptive use and in some premenopausal women using pills, positive effects may result.

Plasma Lipid Levels. A "perfect" hormonal method of birth control would neither increase plasma levels of total cholesterol and low density lipoprotein (LDL) nor reduce high-density lipoprotein cholesterol

(HDL) (45). However, the estrogen component of traditionally formulated oral contraceptives usually raises HDL-cholesterol and triglycerides levels (18) while the progestin component has the opposite effect and tends to lower HDL-cholesterol (18). The importance of such changes in the genesis of arterial vascular disease in users of oral contraceptives is not clear, but presents some cause for concern (45). Although a definitive study examining these concerns has not been conducted, it is generally believed that plasma lipid level changes are likely related to the specific type and dose of progestin employed (7). For example, one study comparing two groups of women taking triphasic formulations (Ortho-Novum® 7/7/7 and Triphasil®) with non-contracepting controls found significant increases in total plasma cholesterol, LDL-cholesterol, and triglycerides levels after 6-months of use (45). Triglyceride levels declined by 12-months, but total- and LDL-cholesterol levels maintained these elevations at one year. HDL-cholesterol was not significantly different after 6- or 12-months of use. Although these researchers found statistically significant differences between women on pills compared to nonusers, all values were within acceptable clinical or normal ranges (45). Thus, the authors conclude that any contribution to increased atherogenesis by either formulation is highly unlikely.

A recent review of more than 50 clinical studies employing DOCA report that this new formulation did not interfere with estrogen's effects on lipoprotein metabolism (13). Although data suggest that statistically significant increases in HDL-cholesterol were found, LDL-cholesterol remained unchanged or demonstrated a slight reduction (13). Another study examining nine groups of women using different oral contraceptives with non-contracepting controls found that levels of LDL-cholesterol were reduced by 14% in those taking pills containing desogestrel and by 12% in those taking low-dose norethindrone (44). Furthermore, these researchers found that the pills traditionally prescribed by the military (NOCA), which contain high-dose norethindrone, did not affect HDL-cholesterol levels, whereas those taking DOCA had increased their HDL by 12% (46). However, duration of oral contraceptive use in this study varied from 3-months to 4-years rendering specific conclusions difficult to interpret.

Conflicting findings on plasma lipid levels among DMPA users have been reported (12). In one study examining the long-term use (5-12 years) of several different contraceptive methods, DMPA caused a moderate decrease in triglycerides, HDL-cholesterol, and apoproteins, whereas estrogen-dominant pills (2 mg norethisterone, 0.1 mg mestranol) increased these same parameters (47). Some investigators have concluded that long-term use of this agent includes some change in lipid metabolism that would be considered a risk factor for atherosclerosis (48).

Technical Objectives

The broad aim of this proposal is to provide critical data on contraceptive outcomes that may be used to generate reproductive healthcare guidelines for servicewomen who have varying needs depending on their military assignment. To accomplish this goal, we are using a prospective, longitudinal design, to compare outcomes among three different methods of contraception (NOCA, DOCA, and DMPA) and are recruiting participants from both military and civilian sites. Use of a nonmilitary site allows us to collect data from women whose health status and reproductive needs are likely to mirror those of reservists and new recruits. Each contraceptive condition will be comprised of approximately 150 women aged 18 to 33 years: one half are being recruited from active-duty servicewomen from one of five military bases in San Antonio and receive their care at Wilford Hall Medical Center, San Antonio, Texas and the remaining half are solicited from women in the greater Galveston-Houston area and receive their at either UTMB's Maternal and Child Health clinic in Galveston, Texas, or a satellite clinic in Webster, Texas. All potential civilian women must meet entry standards for the Armed Forces. All study participants are being assessed after 3-, 6-, 12-, 18-, and 24 months of contraceptive use.

At follow-up visits, subjects complete standardized measures of dysmenorrhea, menstrual pain, medical side-effects and method satisfaction, and submit completed monthly menstrual calendars. Physical examinations are performed by a nurse practitioner or physician at entrance into the study and after 12- and 24-months of continuous contraceptive use. In addition, bone density measurements (lumbar spine and femoral neck) using dual x-ray absorptiometry (DEXA) are obtained at baseline and the 24-month

assessment, while lipid levels are being assessed at baseline and after 12- and 24-months of contraceptive use. DMPA participants return to the clinic at 9, 15, and 21 months to receive an injection only. The specific technical objectives of this study are to determine, at the conclusion of 2 years, which of these three methods:

1. has the highest rate of continuation;
2. has the highest level of user satisfaction;
3. most effectively reduces the occurrence and severity of dysmenorrhea;
4. most effectively decreases the number of bleeding days per 90-day reference period;
5. has the lowest user failure rate resulting in pregnancy;
6. minimizes bone density loss;
7. minimizes changes in lipoprotein levels; and
8. minimizes the occurrence medical side-effects.

Data will be analyzed employing repeated measures multivariate statistical tests so that (1) trends in outcomes over 24 months of contraceptive use can be examined; (2) comparisons of outcomes at specific points in time (6, 12, and 24 months) may be performed; and (3) main effects for method, time, recruitment site, and their interactions can be evaluated. The results of these analyses will help determine the safest, most convenient, and most effective contraception for servicewomen in various phases of duty, i.e., deployed and nondeployed. For example, women who are deployed for two years may experience more contraceptive and noncontraceptive benefits (few bleeding days) as well as greater long-term satisfaction with an injectable contraceptive as compared to an oral contraceptive. In contrast, non-deployed servicewomen with severe dysmenorrhea may experience the greatest relief from DOCA, and hence have reduced absenteeism.

Body

This final report details the specific activities that have occurred during Year 5 of funding (September 23, 2000 through September 22, 2001). According to our Statement of Work, there are a total of five major objectives. All tasks in Objectives one and two were initiated and completed during the first 36 months of the granting period and are not reported in this summary. Major objectives three and four were substantially completed during year four and are not reported in this summary. Final 24 month visits

and data analysis were accomplished during year 5 and tasks 4, 5, 8 and 9 of Objective 4 were completed in Year 5. They are addressed in this report. Objective 5 is preparation of a final summary report and is respectfully submitted here.

Objective 1: Implement the study protocol.

This objective and tasks 1 – 6 were completed in year 1 of funding and reported in the first summary report.

Objective 2: Establish the three contraceptive cohorts: users of norethindrone-containing pills (NOCA), desogestrel –containing pills (DOCA), and DMPA.

This objective and tasks 1 through 7 were completed in year 3 of funding and reported in the third summary report.

Objective 3: Complete required follow-up medical assessments, laboratory tests, and self-report and satisfaction measures at each visit.

This objective and tasks 1 through 10 were completed in year 4 of funding and reported in the fourth summary report.

Objective 4: Analyze study data

This objective involves quantifying study results. There were five tasks completed for this objective in year 4 and four tasks for year 5. Tasks completed in year five are: 4; 4) perform all data entry and verification of study data; 5) reconcile out-of range and inconsistent data elements to insure accuracy of the study data; 8) complete all data entry, range checks, and perform final analyses; and 9) prepare and present reports.

Task 4. ***Perform all data entry and verification of study data.*** Software programs to electronically scan computer-ready questionnaires of the four self-report measures were completed in year 3. Data entry and verification for all data up to 12 months was completed in year 4. Twenty-four month data was entered

and verified in year 5. Data entry began in year 4 and the final two hundred and thirty-eight menstrual calendars were coded and entered in year 5.

Task 5. ***Reconcile out-of-range and inconsistent data elements to insure accuracy of study data.*** All forms are visually inspected as the subject completes the form to insure the accuracy of collected data. Out of-range evaluation is conducted at the time the visit-specific databases (baseline, 3-, 6-, 12-, 18-, and 24-month) are assembled. Out of range evaluation has been completed on all data. The final twenty-nine visits were completed in year 5. The scanning of the 24-month data is completed and reconciliation of missing data is done.

Task 8. ***Complete all data entry, range checks, and perform final analyses.*** Data entry and verification for all data up to 24 months has been completed. Final analyses are complete.

Task 9. ***Preparation and presentation of reports.*** To date one paper has been published, "A Prospective, Controlled Study of the Effects of Hormonal Contraception on Bone Mineral Density." Obstetrics & Gynecology, 98(4): 576-582, October 2001. A copy of this paper can be found in Appendix A. A second paper on bone mineral density results after 24 months of contraceptive use is in preparation. Another paper in preparation is on bleeding patterns, dysmenorrhea and other side effects of hormonal contraceptives. All data has been analyzed and writing of this paper is currently taking place. Selected data tables for these manuscripts are included in reportable outcomes. Additional analyses of data to be used in the two manuscripts in preparation not discussed in reportable outcomes are included in Appendix B. All data presented in outcomes and appendix B are unpublished at this point in time.

Prior to publication a draft of the Obstetrics and Gynecology paper was sent to Commander; US Army Medical Research and Material Command, ATTN: MCMR-RMI-S, 504 Scott Street, Fort Detrick, Maryland 21702-5012. A statement of support by the US Army Medical Research and Material Command was included along with other required statements. This protocol will be followed for the remaining two papers in preparation.

Reportable Outcomes

As noted in the original application, the specific technical objectives of this study are to determine which of these contraceptive methods:

1) has the highest rate of continuation;
2) has the highest level of user satisfaction;
3) most effectively reduces the occurrence and severity of dysmenorrhea;
4) most effectively decreased the number of bleeding days per 90-day reference period;
5) has the lowest user failure rate resulting in pregnancy;
6) minimizes bone density loss;
7) minimizes changes in lipoprotein levels; and
8) minimize the occurrence of medical side effects.

Technical objectives 1, 2, 5, 6, and 8 were reported in year 4. Objectives 3, 4, and 7 are addressed in year 5 as well as 24 month data for objective 6. Multivariate analyses of data by objective is presented below.

OBJECTIVE 3) To determine which method most effectively reduces the occurrence and severity of dysmenorrhea.

Table 1 presents data for the severity of pain associated with menstruation. While dysmenorrhea was greatest at the study onset, levels of dysmenorrhea were low overall, with the highest mean ratings in the 3-4 range (scale range 0-10). Beginning at the 6-month assessment and continuing throughout the 24-month study duration, women using DMPA reported less dysmenorrhea than women using either of the oral contraceptives (all $P \leq .01$). No differences in dysmenorrhea were observed between women using desogestrel versus norethindrone pill formulations (all $P > .57$).

Table 1. Dysmenorrhea scale at baseline, 6, 12, 18, and 24 months by contraceptive method.*

	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P[1]	P[2]	P[3]
Baseline	3.4 ± 0.5 (N= 100)	3.6 ± 0.5 (N= 94)	3.4 ± 0.6 (N = 89)	.99	.99	.99
6-months	1.2 ± 0.4 (N = 81)	2.7 ± 0.4 (N = 85)	2.2 ± 0.5 (N = 76)	<.01	.01	.62
12-months	0.5 ± 0.5 (N = 59)	2.5 ± 0.5 (N = 69)	2.2 ± 0.5 (N = 64)	<.01	<.01	.99
18-months	0.0 ± 0.6 (N = 40)	1.8 ± 0.6 (N = 60)	1.7 ± 0.6 (N = 48)	<.01	<.01	.99

24-months	0.0 ± 0.4 (N = 37)	1.8 ± 0.4 (N = 59)	1.4 ± 0.4 (N = 40)	<.01	<.01	.57

P¹ = Depo compared to Ortho-Cept
P² = Depo compared to Ortho-Novum
P³ = Ortho-Novum compared to Ortho-Cept
* means adjusted for effects of age.

OBJECTIVE 4) To determine which method most effectively decreases the number of bleeding days per 90-day reference period.

The total number of bleeding/spotting days per 90-day reference period are depicted in Table 2. During the first reference period, no statistically reliable differences in bleeding patterns were observed across the three groups. Beginning with the second reference period, however, women using DMPA experienced fewer days of bleeding/spotting as compared to women using either the desogestrel ($P<.01$) or the norethindrone ($P<.05$) pill formulation. This pattern is consistent and significant ($P<.01$) throughout the remaining reference periods reported in this study. Women who reported experiencing a greater number of bleeding/spotting days were more likely to discontinue use of DMPA ($P<.02$). On average, women who discontinued DMPA by the second reference period bled for 37.8 days during the first reference period while women who continued using the method reported bleeding an average of 19.1 days during the first reference period. Women who continued to use DMPA generally achieved amenorrhea after about 14 months of use.

Table 2. Total number of bleeding/spotting days by reference period.*

Reference Period	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P¹	P²	P³
1	23.7 ± 3.9 (N = 101)	17.1 ± 3.7 (N = 95)	16.3 ± 4.1 (N = 90)	.11	.05	.99
2	9.8 ± 2.2 (N = 78)	16.9 ± 2.2 (N = 74)	14.3 ± 2.3 (N = 66)	<.01	.05	.50
3	6.7 ± 2.1 (N = 62)	18.4 ± 2.0 (N = 66)	15.1 ± 2.1 (N = 59)	<.01	<.01	.13
4	5.9 ± 1.7 (N = 56)	18.5 ± 1.6 (N = 58)	15.1 ± 1.8 (N = 50)	<.01	<.01	.05
5	2.1 ± 1.6 (N = 47)	16.1 ± 1.5 (N = 61)	13.8 ± 1.7 (N = 43)	<.01	<.01	.19
	1.5 ± 1.5	16.2 ± 1.4	14.0 ± 1.6			

6	(N = 40)	(N = 59)	(N = 39)	<.01	<.01	.28
7	1.2 ± 1.2 (N = 22)	17.1 ± 1.2 (N = 25)	13.8 ± 1.2 (N = 19)	<.01	<.01	.01

P[1] = Depo compared to Ortho-Cept
P[2] = Depo compared to Ortho-Novum
P[3] = Ortho-Novum compared to Ortho-Cept
means adjusted for effects of age.

Data depicting the total number of days of spotting-only by reference period is presented in Table 3. For approximately the first 9 months of contraceptive use, women using DMPA experienced a greater number of spotting days than women using the desogestrel ($P<.01$) or norethindrone ($P<.03$) pill formulations. Virtually no spotting occurred in women using either pill formulation after the first few months.

Table 3. Total number of spotting only days by reference period.*

Reference Period	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P[1]	P[2]	P[3]
1	8.6 ± 2.2 (N = 101)	1.3 ± 2.1 (N = 95)	3.0 ± 2.3 (N = 90)	<.01	<.01	.99
2	7.2 ± 1.8 (N = 78)	0.1 ± 1.7 (N = 74)	0.9 ± 1.9 (N = 66)	<.01	<.01	.99
3	3.5 ± 1.1 (N = 62)	0.1 ± 1.1 (N = 66)	1.1 ± 1.2 (N = 59)	<.01	.03	.81
4	1.2 ± 0.5 (N = 56)	0.5 ± 0.5 (N = 58)	1.2 ± 0.6 (N = 50)	.42	.99	.43
5	0.8 ± 0.3 (N = 47)	0.6 ± 0.3 (N = 61)	1.3 ± 0.3 (N = 43)	.91	.26	.02
6	0.7 ± 0.4 (N = 40)	0.0 ± 0.4 (N = 59)	0.6 ± 0.5 (N = 39)	.18	.99	.33
7	0.0 ± 0.4 (N = 22)	0.0 ± 0.4 (N = 25)	0.3 ± 0.4 (N = 19)	.99	.99	.64

P[1] = Depo compared to Ortho-Cept
P[2] = Depo compared to Ortho-Novum
P[3] = Ortho-Novum compared to Ortho-Cept
means adjusted for effects of age.

Bleeding patterns were characterized by prolonged consecutive days of bleeding among DMPA users as compared to pill users during the first reference period (both $P<.01$). See Table 4. During the next 3 reference periods, women using DMPA experienced menstrual bleeding patterns similar to the pill groups

until reference period 5, when women in the pill groups continued to bleed for an average of 4-5 days while women comprising the DMPA group reported, on average, only about a single day of bleeding ($P<.01$).

Table 4. Longest bleeding/spotting episode by reference period.*

Reference Period	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P[1]	P[2]	P[3]
1	20.2 ± 3.5 (N = 101)	5.8 ± 3.3 (N = 95)	6.1 ± 3.6 (N = 90)	<.01	<.01	.99
2	7.5 ± 1.6 (N = 78)	5.6 ± 1.6 (N = 74)	4.9 ± 1.7 (N = 66)	.50	.17	.99
3	3.8 ± 1.1 (N = 62)	5.6 ± 1.1 (N = 66)	5.0 ± 1.2 (N = 59)	.19	.58	.99
4	4.2 ± 1.1 (N = 56)	6.0 ± 1.1 (N = 58)	5.1 ± 1.2 (N = 50)	.16	.99	.95
5	1.5 ± 0.7 (N = 47)	5.2 ± 0.7 (N = 61)	4.5 ± 0.8 (N = 43)	<.01	<.01	.82
6	1.0 ± 0.6 (N = 40)	5.2 ± 0.6 (N = 59)	4.4 ± 0.6 (N = 39)	<.01	<.01	.32
7	0.0 ± 0.5 (N = 22)	5.2 ± 0.5 (N = 25)	4.5 ± 0.5 (N = 19)	<.01	<.01	.36

P[1] = Depo compared to Ortho-Cept
P[2] = Depo compared to Ortho-Novum
P[3] = Ortho-Novum compared to Ortho-Cept
means adjusted for effects of age.

OBJECTIVE 6) To determine which method minimizes bone density loss.

Bone mineral density data from 24 month visits was analyzed and is shown in Table 5. DMPA users showed a 5.53% loss in bone density over 24 months as compared to baseline. Oral contraceptive users, norethindrone pills or desogestrel pills, demonstrated a 2.45% loss from baseline and 1.03% loss from baseline respectively. These data show that different methods of hormonal contraception have significantly different effects on BMD after two years of use. A manuscript is in preparation to report these findings in a peer-reviewed journal.

Table 5. Percent Change in Lumbar Spine Bone Mineral Density by Contraceptive Method Baseline-24 Months.

Method	*n*	Covariate-adjusted mean percent change	SEM	95% CI for mean
Norethindrone pill	27	-1.03	1.14	-3.30,1.25

Desogestrel pill	42	-2.45	1.01	-4.46,-0.44
DMPA	33	-5.53	1.13	-7.78,-3.28

SEM = standard error of the mean, CI=confidence interval, DMPA=depo medroxyprogesterone acetate
Covariates included in the model: race/ethnicity, site, smoking status, exercise status, body mass index, calcium intake, and age.

OBJECTIVE 7) To determine which method minimizes changes in lipoprotein levels.

Blood was collected and lipoprotein levels determined; however, due to an error in protocol the data is not publishable. Women were not instructed to fast before coming to their appointment.

Key Research Accomplishments

During this final year, we have accomplished the following tasks:

- Completed the 24 month visits on all subjects.
- Completed data entry, verification and cleaning of 24-month visits.
- Completed analyses of data up to 24 months.
- Published a paper entitled, "A prospective, Controlled Study of the Effects of Hormonal Contraception on Bone Mineral Density," Obstetrics & Gynecology 98(4): 576-582, October 2001.
- Second manuscript on Bone Mineral Density results after 24 months of contraceptive use is in preparation.
- Analyses completed for third manuscript in preparation on bleeding patterns, dysmennorhea and other side effects of hormonal contraception.

Final Bibliography of Publications and Meeting Abstracts

- Berenson AB, Radecki CM, Grady JJ, Rickert VI, Thomas A. A Prospective, Controlled Study of the Effects of Hormonal Contraception on Bone Mineral Density. *Obstetrics&Gynecology* 2001:98(4):576-582.
- **A prospective study of the effects of oral and injectable contraception on bone mineral density** was presented orally at American College of Obstetricians and Gynecologists on May 22, 2000.

- **Condom practices prior to and after initiation of hormonal contraception"** was presented at the annual meeting of Central Association of Obstetricians and Gynecologists October 21, 2000.
- **A prospective study of the effects of two years of oral and injectable contraception on bone mineral density.** In preparation. 2001.
- **Bleeding Patterns, Dysmenorrhea and other side effects of hormonal contraceptives.** In preparation. 2001.

List of Personnel

The following people received pay at sometime during the five years of this research effort:

Abbey Berenson, MD

Angelyn Thomas, MD

James Grady, DRPH

Vaughn Rickert, PSYD

Joanie Bessman

Barbara DeLeon

Brenda Stewart

Conclusion

The final year has been an active and successful termination of the project. Twenty-four month study visits for all subjects have been completed. Data entry and verification for all data has been completed. Analyses have been completed for all data. One paper has been published and two others are in preparation.

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A Prospective, Controlled Study of the Effects of Hormonal Contraception on Bone Mineral Density

Abbey B. Berenson, MD, Carmen M. Radecki, PhD, James J. Grady, DRPH, Vaughn I. Rickert, PSYD, and Angelyn Thomas, MD

OBJECTIVE: To compare the effect of depot medroxyprogesterone acetate (DMPA) and two types of oral contraceptives (OC) on bone mineral density (BMD) among women 18–33 years of age with those not using hormonal contraception.

METHODS: Data from 155 women were analyzed. Depot medroxyprogesterone acetate was administered to 33 women; 63 women who chose oral contraception were randomly assigned to receive either a norethindrone-containing pill (n = 28) or a desogestrel-containing pill (n = 35). Fifty-nine women who did not use hormonal contraception served as controls. Lumbar spine BMD was determined using dual-energy x-ray absorptiometry at baseline and after 12 months of contraceptive use. We analyzed method-related percent change in BMD while controlling for body mass index, calcium intake, exercise, and smoking. We had approximately 90% power to detect a 2.5% difference between any two groups.

RESULTS: Users of DMPA experienced a mean BMD loss of 2.74% over 12 months compared with controls who sustained a 0.37% loss (P = .01). Users of OCs generally demonstrated a gain (2.33% for norethindrone-containing pills, 0.33% for desogestrel-containing pills), which was different from controls among users of norethindrone-containing pills (P = .01), but not among users of desogestrel-containing pills (P = .99). Observed changes in BMD among DMPA users differed from women who used either type of pill (P < .002).

CONCLUSION: Depot medroxyprogesterone acetate has an adverse effect on BMD, in comparison with OCs or nonhormonal methods, when used for 12 months. Results must be interpreted cautiously until it is determined whether these effects endure or are reversible. (Obstet Gynecol 2001;98:576–82. © 2001 by the American College of Obstetricians and Gynecologists.)

Recent studies have suggested that use of depot medroxyprogesterone acetate (DMPA) during the reproductive years may cause or accelerate bone loss. In a cross-sectional study, Cundy et al noted that DMPA users had a lumbar spine bone mineral density (BMD) that was 7.2% lower than that of matched controls.[1] Cromer et al noted a 3.1% reduction in lumbar BMD among eight adolescents who used DMPA for 2 years,[2] and Scholes et al observed an adverse relationship between DMPA use and BMD among young women.[3] Several other investigations outside of the United States have associated use of DMPA with decreased bone density in the lumbar spine,[4,5] as well as several regions of the hip (Ward's triangle, trochanter, femoral neck),[5] and the distal forearm.[6] However, no prospective study has been published, comparing adult DMPA users with women using no hormonal contraception, which controlled for demographic and behavioral factors believed to affect BMD. Thus, the independent effects of DMPA use on BMD among adult women remain unclear.

Similarly, it is not clear whether use of birth control pills during the reproductive years affects BMD. Some studies have shown that use of oral contraceptives (OC) has a beneficial effect on BMD,[7–9] whereas others report no effect.[10,11] Findings from these studies are difficult to interpret for several reasons. First, some studies included users of pills containing 50–100 μg of ethinyl estradiol (E2),[12,13] formulations that are currently unavailable or rarely prescribed. Others combined users of different pill formulations or failed to specify the pill formulation.[7–11] Studies are also limited by small sample sizes[2,14] and

From the Departments of Obstetrics and Gynecology and Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, Texas; and Wilford Hall Medical Center, San Antonio, Texas.

Dr. Rickert is currently at the Department of Pediatrics, The Mount Sinai School of Medicine, New York, New York; and Dr. Thomas is in private practice in Oakland, California.

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minimal consideration of behavioral confounders.[9,14] Finally, many studies on OCs did not include a control group.[9,15,16]

The purpose of this study was to assess the independent effect of DMPA and two different types of OC on BMD among women 18–33 years of age compared with those not using hormonal contraception over a 12-month interval.

MATERIALS AND METHODS

All women recruited between May 16, 1996, and January 20, 1999, who had undergone a baseline bone scan as part of a larger contraceptive study, were eligible to participate. Subjects were between 18 and 33 years of age and white, black, Asian, or Hispanic. Because of the funding source (Department of Defense), all women were required to meet minimal criteria for entry into the Armed Forces (graduated high school or had GED, no felony arrests, within 36% of ideal body weight for height, and free of medical conditions or physical disabilities that would preclude satisfactory completion of military training). Women who were currently pregnant or breastfeeding, had received an injection for contraception during the past 6 months, or were taking birth control pills within the past month, or had a medical contraindication to hormonal contraception were not eligible. Subjects were recruited in person or in response to an advertisement at one of two sites: Wilford Hall Medical Center (WHMC) in San Antonio, Texas, or the Maternal and Child Health Clinic at the University of Texas Medical Branch (UTMB), Galveston, Texas. In addition, 71 women not using hormonal contraception were recruited at UTMB to serve as controls. This study was approved by the Institutional Review Boards of the Department of Defense, WHMC, and UTMB.

After obtaining informed, written consent, each subject was allowed to select the type of contraception that she would use for the duration of the study. Women who preferred injectable contraception received 150 mg of DMPA every 3 months, whereas those who chose oral contraception were randomly assigned to receive either pills containing 0.035 mg of ethinyl E2 and 1.0 mg of norethindrone or pills containing 0.030 mg of ethinyl E2 and 0.15 mg of desogestrel. Pills were referred to by the color names "green" (the desogestrel formulation) or "red" (the norethindrone formulation) and were deidentified by a research assistant who eliminated package labeling. Randomization was carried out through the use of a random numbers table, which assigned the next eligible patient who chose to use OCs to either the "green" or the "red" formulation. Women who did not wish to use hormonal birth control were recruited to serve as controls. Controls were frequency matched on age and race/ethnicity to the entire sample of hormonal contraceptive users.

At the initial visit, height and weight were measured from which body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Demographic information and medical history were recorded. Cigarette use was recorded as a dichotomous variable: yes (smoked occasionally, regularly in the past, or regularly now) or no (never smoked, smoked only once or twice in the past). Whether or not the individual engaged in weight-bearing and/or high-impact exercise as part of a regular exercise program was recorded as a dichotomous variable (yes/no). To determine calcium consumption, trained research personnel assisted women with recalling and recording all foods and beverages consumed during the 24 hours before the baseline study visit. Appropriate cues and prompts were given to help women with recall, and writing assistance was provided as necessary. Calcium intake was computed using Menu Mizar 3.0 for Windows (Menu Systems, Ruffs Dale, PA).

Bone mineral density of the anterior-posterior lumbar spine (L1–L4) was determined using dual-energy x-ray absorptiometry at baseline and after 12 months of contraceptive use. All baseline scans were performed within 2 months of initiation of hormonal contraception. Follow-up scans were performed on all women between 10 and 14 months after the baseline scan. In addition, follow-up scans for hormonal contraceptive users were performed within 2 months of their 1-year anniversary of initiating contraception. Bone mineral density measurement was performed using a single machine at each study site. Scans at UTMB were performed using a Hologic QDR 1000-W (Hologic, Waltham, MA) bone densitometer, whereas those at WHMC were obtained with a Lunar DPX (Lunar, Madison, WI). Direct comparison of measured BMD values between the two sites was limited by the use of machines from different manufacturers. However, experts have shown strong correlations across Hologic and Lunar machines when percentage change in BMD is used in longitudinal studies as a measure of lumbar spine BMD changes.[17]

Short-term precision was evaluated to examine the reproducibility of BMD outcomes. To estimate precision, 20 subjects at UTMB and 10 at WHMC were randomly selected to undergo two consecutive scans at their 12-month visit, with an approximate interscan interval of 10–20 minutes. The coefficient of variation was computed as the root-mean-square averages of standard deviations (SD) of the repeated measurements.[18] In vivo precision was less than 1% for the only technician at WHMC and 1.2% for the primary technician at UTMB.

Table 1. Unadjusted Mean Percent Change Bone Mineral Density by Contraceptive Method

Contraceptive method	*n*	Mean percent change lumbar spine BMD	SD
Norethindrone pill	28	+1.88	2.99
Desogestrel pill	35	+0.05	2.62
DMPA	33	−2.83	3.01
Control	59	−0.95	3.78

BMD = bone mineral density; DMPA = depot medroxyprogesterone acetate; SD = standard deviation.

Continuous variables are expressed as means ± SD. Group comparisons for these variables were conducted using analysis of variance or independent group *t* tests. Group differences in categorical variables were analyzed using χ^2 or Fisher exact test. A two-sided significance level of .05 was used to determine statistical significance. Separate analyses were conducted at each site on the actual BMD values (g/cm^2) to estimate mean changes from baseline and conduct group comparisons using analysis of covariance (ANCOVA). Our primary outcome was change in BMD over the follow-up interval, which was computed as the mean percent change from baseline using the formula: (follow-up BMD − baseline BMD)/baseline BMD × 100. An ANCOVA was performed on percent change BMD, controlling for pertinent behavioral (smoking, calcium intake, weight-bearing exercise) and demographic (race/ethnicity, age, BMI) factors related to BMD. Group mean percent changes in lumbar spine BMD, adjusted for covariates, and Bonferroni adjusted 95% confidence intervals for group comparisons were estimated using ANCOVA. Bonferroni-adjusted *P* values from these models are presented for pairwise comparisons of groups.

A post-hoc power analysis using observed mean differences and SDs demonstrated that this study had greater than 90% power to detect differences between the DMPA and pill groups, and between the norethindrone-containing pill group and the control group. There was 71% power to detect differences between the two pill groups and between DMPA users and controls, and only 30% power to detect the difference between controls and users of desogestrel-containing pills. Power calculations were based on the two-sample *t* test for unequal *n* using a two-sided significance level of .05. The estimate for the SD was the average for the two groups being compared (see Table 1).

RESULTS

A total of 275 women who met all inclusion criteria were enrolled in the study. Of these, 96 chose injectable contraception and were administered DMPA, whereas 179 women elected to initiate oral contraception and were randomly assigned to receive either norethindrone-containing ($n = 87$) or desogestrel-containing ($n = 92$) pills. Thirty-nine percent (107 of 275) of women discontinued their hormonal method before their 12-month visit. Of the 168 women who continued their method, 31 failed to undergo a bone scan at 12 months because of scheduling conflicts, whereas 37 additional women obtained a scan, but failed to do so within the required window (±31 days of their 12-month anniversary date). Thus, a total of 100 users of hormonal contraception were available for analysis. Final analyses were conducted on 96 users of hormonal contraception (four women were eliminated from analysis as statistical outliers with 12-month BMD changes greater than three SD from the sample mean). In addition, 59 of the 71 controls (83%) received a 12-month bone scan within the required window and were included as a comparison group in the final analyses. Women who dropped out of the study did not differ from the 155 women included in the final analyses on contraceptive method ($P = .71$), smoking ($P = .73$), exercise, ($P = .99$), calcium intake ($P = .98$), race/ethnicity ($P = .08$), or BMI ($P = .68$). Those who dropped out were, on average, 1.6 years younger than those who remained in the study ($P < .001$) and were more likely to have been recruited at WHMC ($P < .001$).

There were no significant differences between the four contraceptive groups in their characteristics (Table 2), although women who selected an oral method of birth control were significantly less likely to report smoking cigarettes than those who used DMPA or nonhormonal methods ($P = .02$).

Using the actual BMD values (g/cm^2), separate ANCOVAs were performed on BMD data obtained at UTMB and WHMC because of the use of DXA machines from different manufacturers. Both sites revealed similar group patterns in BMD change after 1 year (Table 3). Women using DMPA, on average, experienced a loss in bone density. Using data from UTMB only, the results of the ANCOVA revealed that the loss in BMD among DMPA users was significantly greater than that observed among controls ($P = .03$). Women using OCs experienced slight gains or no change in BMD at both sites. Bone mineral density changes among users of desogestrel-containing pills compared with users of norethindrone-containing pills did not differ at UTMB ($P = .39$) or WHMC ($P = .95$).

Initial analyses were conducted to evaluate potential interaction effects in our ANCOVA models. Separate models including all main effects and the interactions (method × site), (method × smoking status), and (method × age) were tested. None of the interaction terms

Table 2. Descriptive Data at Baseline by Contraceptive Method

Variable	Norethindrone pill (n = 28)	Desogestrel pill (n = 35)	DMPA (n = 33)	Control (n = 59)	P
Age (y)					.16
Mean ± SD	26.2 ± 3.9	25.7 ± 4.1	24.0 ± 4.0	25.6 ± 4.3	
Range	20–33	19–33	18–33	18–33	
Race/ethnicity n (%)					.85
White (n = 111)	18 (64.3)	25 (71.4)	26 (78.8)	42 (71.2)	
Black (n = 21)	6 (21.4)	3 (8.6)	4 (12.1)	8 (13.6)	
Hispanic (n = 21)	4 (14.3)	6 (17.1)	3 (9.1)	8 (13.6)	
Asian (n = 2)	0 (0.0)	1 (2.8)	0 (0.0)	1 (1.7)	
Smoking n (%)					.02
Yes	5 (17.9)	9 (25.7)	17 (51.5)	25 (42.4)	
Weight-bearing exercise n (%)					.27
Yes	13 (46.4)	13 (37.1)	14 (42.4)	16 (27.1)	
Dietary calcium (mg/day)*					.69
Mean ± SD	537 ± 359	634 ± 466	546 ± 303	548 ± 373	
Range	18–1403	100–2130	41–1170	86–1810	
Body mass index					.52
Mean ± SD	22.7 ± 2.6	23.4 ± 3.0	22.4 ± 2.9	22.5 ± 3.0	
Range	18.6–27.8	17.2–29.9	16.8–28.0	16.9–30.0	

Abbreviations as in Table 1.
Plus-minus values are means ± SD.
* Values based on 24-h dietary recall.

were significant (P = .94, P = .11, and P = .94, respectively). Analysis of covariance was performed on percent change BMD, with method, race/ethnicity, site, smoking, and exercise status included as fixed factors, and calcium intake, BMI, and age included as continuous covariates. All covariates remained in the model regardless of their P value. The model evidenced a statistically significant effect only for contraceptive method [$F(3,142) = 11.43$, $P < .001$]. Users of DMPA experienced an average loss of 2.7% in BMD over the 12-month interval compared with controls who sustained a 0.37% mean loss (P = .01, Table 4). On average, users of both types of birth control pills demonstrated a gain, with users of norethindrone-containing pills experiencing a 2.33% gain, and users of desogestrel-containing pills demonstrating a 0.33% gain in BMD. Table 5 presents 95% confidence intervals for pairwise differences in percent change in BMD between the contraceptive groups. The gain among users of pills was significantly different from controls for users of norethindrone-containing pills (P = .01), but not for users of desogestrel-containing pills (P = .99). Mean changes in BMD significantly differed between DMPA users and women who used either type of birth control pill (both $P < .002$).

DISCUSSION

We observed that use of DMPA for 12 months has an adverse effect on BMD, compared with OCs or nonhormonal methods. On average, women who used DMPA experienced approximately a 2.7% loss in BMD com-

Table 3. Mean Bone Mineral Density Changes (g/cm^2) of the Lumbar Spine After 1 Year by Site and Method

	n	Mean covariate-adjusted change in BMD (g/cm^2)	SEM	95% CI for mean
UTMB (Hologic)	116			
Norethindrone pill	13	+0.024	0.013	−0.002, 0.049
Desogestrel pill	22	+0.002	0.011	−0.021, 0.024
DMPA	22	−0.030	0.012	−0.053, −0.007
Control	59	−0.006	0.009	−0.024, −0.013
WHMC (Lunar)	39			
Norethindrone pill	15	+0.014	0.017	−0.021, 0.049
Desogestrel pill	13	−0.001	0.017	−0.036, 0.035
DMPA	11	−0.028	0.016	−0.060, 0.004

BMD = bone mineral density; SEM = standard error of the mean; CI = confidence interval; UTMB = University of Texas Medical Branch; DMPA = depot medroxyprogesterone acetate; WHMC = Wilford Hall Medical Center.
Covariates included in the model: race/ethnicity, smoking status, exercise status, body mass index, calcium intake, and age.

Table 4. Percent Change in Lumbar Spine Bone Mineral Density by Contraceptive Method

	n	Covariate-adjusted mean percent change	SEM	95% CI for mean
Norethindrone pill	28	+2.33	0.91	0.53, 4.12
Desogestrel pill	35	+0.33	0.82	−1.30, 1.96
DMPA	33	−2.74	0.86	−4.44, −1.05
Control	59	−0.37	0.82	−1.98, 1.25

Abbreviations as in Tables 1 and 3.

Covariates included in the model: race/ethnicity, site, smoking status, exercise status, body mass index, calcium intake, and age.

pared with a 0.37% loss in those not using hormonal contraception and small gains among OC users of 0.33% and 2.33%, respectively, for users of desogestrel- and norethindrone-containing pills. The mechanism of the effect of DMPA on BMD is unknown. However, studies have shown that DMPA users have significantly lower serum E2 levels than users of nonhormonal contraception.[15,19] In the absence of adequate levels of estrogen, (postmenopausal, anorexia nervosa, GnRH therapy), bone resorption outstrips formation, and bone mass decreases.[20] Thus, it seems logical that the bone loss associated with DMPA use is caused by hypoestrogenism and a subsequent increase in bone turnover. Alternatively, the decrease in BMD could be related to the exogenous glucocorticoid-like effects of DMPA.[21]

This study compares the effects of two different types of OCs on BMD. Previously, it was not possible to compare the effects of the type of pill on BMD because earlier studies did not specify the type, merged different types, or included only one pill formulation. In contrast, we randomized OC users to a norethindrone-containing or desogestrel-containing pill. A small gain in BMD was noted among users of both types of pills, which was significantly different from controls for norethindrone pills. We did not detect a difference between users of desogestrel pills and controls, which may have been because of insufficient power. In addition, we did not detect a difference between these two pills in their effect on BMD. The lack of a significant difference between the two pill groups in this study suggests that no firm conclusions should be drawn regarding a potential difference between these two types of pills until more data are available.

Table 5. Bonferroni-Adjusted 95% Confidence Intervals for Pairwise Differences in Percent Change Bone Mineral Density

	95% CI for difference
Norethindrone pill-control	0.45, 4.93
Desogestrel pill-control	−1.29, 2.69
DMPA-control	−4.43, −0.32
Norethindrone pill-desogestrel pill	−0.26, 4.25
Norethindrone pill-DMPA	2.72, 7.41
Desogestrel pill-DMPA	0.87, 5.27

Abbreviations as in Tables 1 and 3.

Covariates included in the model: race/ethnicity, site, smoking status, exercise status, body mass index, calcium intake, and age.

Because of the difficulty in randomizing women to a particular contraceptive method, we did allow all subjects to select whether they would use injectable, oral, or a nonhormonal method. In the absence of a randomized design, we carefully inspected the data for evidence of bias (because of self-selection) in the composition of the contraceptive groups. Specifically, we examined group-based differences in age, race/ethnicity, weight-bearing exercise habits, calcium intake, cigarette smoking, and BMI. These analyses were conducted univariately using appropriate statistical tests, and multivariably by conducting analyses of variance that included the relevant interaction terms. Although only smoking status significantly differed by method, we included all behavioral and demographic factors as covariates in our final analysis. Our inclusion of multiple covariates and our choice to apply a Bonferroni correction to evaluate pairwise comparisons between contraceptive groups represents a conservative strategy toward detecting method-related effects on BMD. The contraceptive-related differences we observed in BMD remained significant after controlling for behavioral and demographic correlates such as smoking and age, which have been influential in the broader literature on bone density.

Calcium intake data demonstrated that regardless of the type of contraception they used, few women ingested an adequate amount of calcium. In fact, the daily mean calcium intake among all women was 565 mg (SD = 379). Only 7% of women 18–24 years old ingested the recommended daily amount (1200 mg) for women aged 11–24 years, whereas only 12% of women 25–33 years of age met recommendations for their age group (1000 mg/day).[22] This is particularly disconcerting considering that most women in our study had healthy habits – 61% reported exercising three times per week or more, and none were obese. Thus, it appears that women of reproductive age may not ingest adequate amounts of calcium, even if they engage in other healthy behaviors. This is especially of concern if their contraception places them at risk of bone loss.

This study has limitations that bear mentioning. Ideally, all women would have been scanned on a single bone densitometer. We minimized this shortcoming by first inspecting the pattern of data within each site as differences between measured BMD and as percent change BMD over the study interval. Only upon observation of consistent patterns at UTMB and WHMC did we merge the data from the two sites and report overall percent change in BMD. We also note that most women in this study were white, and all were within 36% of their ideal body weight and had obtained a high school degree. As most women in the United States do not fit this profile, our findings are not readily applicable to the general population. Furthermore, a 39% method discontinuation rate was observed within the12-month study period. This discontinuation rate is similar, and in many cases, lower, than that found in other published studies. For example, among users of various OC formulations, 12-month discontinuation rates have ranged from nearly 36–66%,[23,24] and among users of injectable contraception, 1-year discontinuation rates have ranged from 48–77%.[24–28] Acknowledging that high discontinuation rates temper the conclusions that can be drawn in contraceptive studies, we are careful to apply the findings of this research only to women who continued their contraceptive method for a 1-year period. Finally, we collected data over 12 months only. Additional studies are needed to determine the effects of these methods on BMD compared with controls over longer durations of use.

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Address reprint requests to: Abbey B. Berenson, MD, Department of Obstetrics and Gynecology, University of Texas Medical Branch, 301 University Boulevard, Route 0587, Galveston, TX 77555-0587; E-mail: abberens@utmb.edu.

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Appendix B

Analyses of data to be used in manuscripts in preparation

Table 1. Demographic difference between women using Ortho-Novum, Ortho-Cept, or Depo-Provera.

	Ortho-Novum (red) N = 90	Ortho-Cept (green) N = 95	Depo-Provera N = 101	P
Gravidity	50/90 (55.6%)	40/95 (42.1%)	56/101 (55.4%)	.10
Parity	37/90 (41.1%)	27/95 (28.4%)	38/101 (37.6%)	.17
Race				
Caucasian	69/90 (76.7%)	68/95 (71.6%)	71/101 (70.3%)	.19
African-American	12/90 (13.3%)	12/95 (12.6%)	20/101 (19.8%)	
Mexican American	9/90 (10%)	12/95 (12.6%)	10/101 (9.9%)	
Asian American	0/90 (0%)	3/95 (3.2%)	0/101 (0%)	
Not Married	58/90 (64.4%)	72/94 (76.6%)	70/100 (70%)	.20
Not Enrolled in School	58/90 (64.4%)	56/95 (58.9%)	65/101 (64.4%)	.67
Employed	80/89 (89.9%)	76/91 (83.5%)	91/100 (91%)	.23
Income 0 to $29,999	51/88 (58%)	57/92 (62%)	65/100 (65%)	.61
Last Grade Completed >High school	75/90 (83.3%)	74/95 (77.9%)	78/101 (77.2%)	.53
Non-smokers	73/90 (81.1%)	78/95 (82.1%)	67/101 (66.3%)	.02[1], .01[2], .86[3]
Age	24.52 ± 3.74	25.05 ± 4.38	23.56 ± 3.81	.08[1], .01[2], .38[3]
BMI	22.9 ± 2.76	22.7 ± 3.6	22.5 ± 2.89	.40[1], .79[2], .65[3]

1. Depo compared to Ortho-Novum
2. Depo compared to Ortho-Cept
3. Ortho-Novum compared to Ortho-Cept

Table 2. Hemoglobin and hematocrit levels at baseline, 12 and 24 months by contraceptive method.*

		Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P^1	P^2	P^3
Baseline	HGB	13.4 ± 0.2 (N= 101)	13.5 ± 0.2 (N= 95)	13.4 ± 0.3 (N= 90)	.99	.99	.99
	HCT	39.7 ± 0.5 (N= 101)	39.6 ± 0.5 (N= 95)	39.3 ± 0.6 (N= 90)	.99	.76	.99
12-months	HGB	13.8 ± 0.5 (N= 60)	13.8 ± 0.5 (N= 67)	13.3 ± 0.6 (N= 57)	.99	.81	.75
	HCT	40.6 ± 0.8 (N= 60)	40.1 ± 0.7 (N= 67)	39.4 ± 0.8 (N= 57)	.99	.19	.77
24-months	HGB	13.7 ± 0.3 (N= 22)	13.2 ± 0.3 (N= 41)	13.3 ± 0.3 (N= 23)	.20	.65	.99
	HCT	40.0 ± 1.4 (N=22)	37.8 ± 1.2 (N=41)	36.7 ± 1.4 (N= 23)	.30	.07	.99

P^1 = Depo compared to Ortho-Cept
P^2 = Depo compared to Ortho-Novum
P^3 = Ortho-Novum compared to Ortho-Cept
* means adjusted for effects of age.

Table 3. Average number of bleeding/spotting days per episode by reference period.*

Reference Period	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P¹	P²	P³
1	14.8 ± 2.6 (N = 101)	4.5 ± 2.4 (N = 95)	4.3 ± 2.7 (N = 90)	<.01	<.01	.99
2	6.6 ± 1.5 (N = 78)	4.7 ± 1.5 (N = 74)	4.3 ± 1.6 (N = 66)	.40	.20	.99
3	3.0 ± 0.8 (N = 62)	4.9 ± 0.8 (N = 66)	4.4 ± 0.8 (N = 59)	<.01	.06	.99
4	3.6 ± 0.9 (N = 56)	5.2 ± 0.9 (N = 58)	4.5 ± 1.0 (N = 50)	.08	.70	.90
5	1.1 ± 0.5 (N = 47)	4.6 ± 0.5 (N = 61)	4.1 ± 0.6 (N = 43)	<.01	<.01	.69
6	0.9 ± 0.5 (N = 40)	4.8 ± 0.4 (N = 59)	4.1 ± 0.5 (N = 39)	<.01	<.01	.21
7	0.0 ± 0.3 (N = 22)	4.7 ± 0.3 (N = 25)	4.2 ± 0.4 (N = 19)	<.01	<.01	.33

P¹ = Depo compared to Ortho-Cept
P² = Depo compared to Ortho-Novum
P³ = Ortho-Novum compared to Ortho-Cept
• means adjusted for effects of age.

Table 4. Average number of spotting only days per episode by reference period.*

Reference Period	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P¹	P²	P³
1	7.1 ± 2.1 (N = 101)	1.5 ± 2.0 (N = 95)	2.9 ± 2.2 (N = 90)	<.01	.03	.99
2	3.7 ± 0.9 (N = 78)	0.1 ± 0.9 (N = 74)	0.7 ± 0.9 (N = 66)	<.01	<.01	.99
3	1.7 ± 0.5 (N = 62)	0.0 ± 0.5 (N = 66)	0.4 ± 0.5 (N = 59)	<.01	<.01	.99
4	0.6 ± 0.2 (N = 56)	0.3 ± 0.2 (N = 58)	0.5 ± 0.3 (N = 50)	.31	.99	.92
5	0.7 ± 0.2 (N = 47)	0.5 ± 0.2 (N = 61)	0.8 ± 0.2 (N = 43)	.43	.99	.13
6	0.6 ± 0.3 (N = 40)	0.1 ± 0.3 (N = 59)	0.3 ± 0.3 (N = 39)	.18	.90	.99
7	0.0 ± 0.3 (N = 22)	0.0 ± 0.3 (N = 25)	0.3 ± 0.3 (N = 19)	.99	.52	.14

P¹ = Depo compared to Ortho-Cept
P² = Depo compared to Ortho-Novum
P³ = Ortho-Novum compared to Ortho-Cept
* means adjusted for effects of age.

Table 5. Average number of nonbleeding days per episode by reference period.*

Reference Period	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P[1]	P[2]	P[3]
1	59.4 ± 4.6 (N = 101)	27.0 ± 4.4 (N = 95)	27.4 ± 4.8 (N = 90)	<.01	<.01	.99
2	62.5 ± 4.8 (N = 78)	25.4 ± 4.7 (N = 74)	27.1 ± 5.1 (N = 66)	<.01	<.01	.99
3	84.2 ± 5.8 (N = 62)	24.7 ± 5.5 (N = 66)	26.1 ± 6.0 (N = 59)	<.01	<.01	.99
4	88.0 ± 4.8 (N = 56)	23.7 ± 4.7 (N = 58)	24.3 ± 5.1 (N = 50)	<.01	<.01	.99
5	100.1 ± 4.6 (N = 47)	27.3 ± 4.3 (N = 61)	29.7 ± 4.8 (N = 43)	<.01	<.01	.99
6	99.2 ± 5.4 (N = 40)	26.5 ± 4.9 (N = 59)	27.8 ± 5.5 (N = 39)	<.01	<.01	.99
7	102.6 ± 4.9 (N = 22)	24.1 ± 4.7 (N = 25)	26.4 ± 5.0 (N = 19)	<.01	<.01	.99

Table 8. Total number of nonbleeding days by reference period.*

Reference Period	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P[1]	P[2]	P[3]
1	88.1 ± 4.3 (N = 101)	89.1 ± 4.1 (N = 95)	89.8 ± 4.5 (N = 90)	.99	.99	.99
2	95.0 ± 3.8 (N = 78)	91.4 ± 3.7 (N = 74)	93.3 ± 4.0 (N = 66)	.80	.99	.99
3	103.0 ± 3.6 (N = 62)	92.1 ± 3.4 (N = 66)	94.6 ± 3.7 (N = 59)	<.01	.01	.99
4	107.0 ± 2.7 (N = 56)	90.4 ± 2.6 (N = 58)	92.0 ± 2.8 (N = 50)	<.01	<.01	.99
5	108.1 ± 2.8 (N = 47)	89.5 ± 2.6 (N = 61)	90.1 ± 3.0 (N = 43)	<.01	<.01	.99
6	106.7 ± 3.1 (N = 40)	91.4 ± 2.8 (N = 59)	91.8 ± 3.2 (N = 39)	<.01	<.01	.99
7	106.0 ± 3.9 (N = 22)	89.4 ± 3.8 (N = 25)	90.7 ± 4.0 (N = 19)	<.01	<.01	.99

Table 9. Total number of bleeding/spotting episodes by reference period.*

Reference Period	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P[1]	P[2]	P[3]
1	1.3 ± 0.2 (N=101)	3.6 ± 0.2 (N=95)	3.5 ± 0.2 (N=90)	<.01	<.01	.99
2	.90 ± 0.2 (N=78)	3.6 ± 0.2 (N=74)	3.3 ± 0.2 (N=66)	<.01	<.01	.40
3	0.7 ± 0.2 (N=62)	3.8 ± 0.2 (N=66)	3.5 ± 0.2 (N=59)	<.01	<.01	.24
4	0.6 ± 0.2 (N=56)	3.6 ± 0.2 (N=58)	3.4 ± 0.2 (N=50)	<.01	<.01	.44
5	0.2 ± 0.2 (N=47)	3.4 ± 0.2 (N=61)	3.0 ± 0.2 (N=43)	<.01	<.01	.10
6	0.2 ± 0.2 (N=40)	3.5 ± 0.2 (N=59)	3.3 ± 0.2 (N=39)	<.01	<.01	.59
7	0.4 ± 0.2 (N=22)	3.7 ± 0.2 (N=25)	3.3 ± 0.2 (N=19)	<.01	<.01	.09

P[1] = Depo compared to Ortho-Cept
P[2] = Depo compared to Ortho-Novum
P[3] = Ortho-Novum compared to Ortho-Cept
* means adjusted for effects of age.

Table 10. Total number of non-bleeding intervals by reference period.*

Reference Period	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P¹	P²	P³
1	2.0 ± 0.2 (N = 101)	3.6 ± 0.2 (N = 95)	3.7 ± 0.2 (N = 90)	<.01	<.01	.95
2	2.2 ± 0.2 (N = 78)	3.7 ± 0.2 (N = 74)	3.7 ± 0.3 (N = 66)	<.01	<.01	.99
3	1.9 ± 0.3 (N = 62)	3.8 ± 0.3 (N = 66)	3.8 ± 0.3 (N = 59)	<.01	<.01	.99
4	1.6 ± 0.2 (N = 56)	3.8 ± 0.2 (N = 58)	3.8 ± 0.2 (N = 50)	<.01	<.01	.99
5	1.3 ± 0.2 (N = 47)	3.5 ± 0.2 (N = 61)	3.6 ± 0.2 (N = 43)	<.01	<.01	.99
6	1.2 ± 0.2 (N = 40)	3.4 ± 0.2 (N = 59)	3.6 ± 0.2 (N = 39)	<.01	<.01	.99
7	1.3 ± 0.2 (N = 22)	3.7 ± 0.2 (N = 25)	3.4 ± 0.3 (N = 19)	<.01	<.01	.45

Table 12. Longest non-bleeding interval by reference period.*

Reference Period	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P¹	P²	P³
1	69.8 ± 4.4 (N = 101)	31.5 ± 4.2 (N = 95)	34.4 ± 4.7 (N = 90)	<.01	<.01	.99
2	75.1 ± 4.3 (N = 78)	31.2 ± 4.3 (N = 74)	34.3 ± 4.6 (N = 66)	<.01	<.01	.99
3	90.4 ± 4.9 (N = 62)	28.0 ± 4.7 (N = 66)	29.9 ± 5.1 (N = 59)	<.01	<.01	.99
4	94.5 ± 4.0 (N = 56)	29.0 ± 3.9 (N = 58)	31.0 ± 4.2 (N = 50)	<.01	<.01	.99
5	104.3 ± 4.4 (N = 47)	32.1 ± 4.1 (N = 61)	34.7 ± 4.7 (N = 43)	<.01	<.01	.99
6	101.3 ± 5.1 (N = 40)	32.4 ± 4.6 (N = 59)	32.7 ± 5.2 (N = 39)	<.01	<.01	.99
7	101.1 ± 5.4 (N = 22)	31.0 ± 5.3 (N = 25)	35.3 ± 5.6 (N = 19)	<.01	<.01	.99

Table 13. Range of bleeding/spotting episodes by reference period.*

Reference Period	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P¹	P²	P³
1	0.5 ± 0.2 (N = 101)	2.6 ± 0.2 (N = 95)	2.5 ± 0.2 (N = 90)	<.01	<.01	.99
2	0.5 ± 0.2 (N = 78)	2.7 ± 0.2 (N = 74)	2.4 ± 0.2 (N = 66)	<.01	<.01	.31
3	0.4 ± 0.2 (N = 62)	2.8 ± 0.2 (N = 66)	2.5 ± 0.2 (N = 59)	<.01	<.01	.13
4	0.3 ± 0.2 (N = 56)	2.6 ± 0.2 (N = 58)	2.4 ± 0.2 (N = 50)	<.01	<.01	.33
5	0.0 ± 0.2 (N = 47)	2.4 ± 0.2 (N = 61)	2.1 ± 0.2 (N = 43)	<.01	<.01	.10
6	0.1 ± 0.2 (N = 40)	2.5 ± 0.2 (N = 59)	2.4 ± 0.2 (N = 39)	<.01	<.01	.99
7	0.0 ± 0.2 (N = 22)	2.0 ± 0.2 (N = 25)	1.6 ± 0.2 (N = 19)	<.01	<.01	.14

P¹ = Depo compared to Ortho-Cept
P² = Depo compared to Ortho-Novum
P³ = Ortho-Novum compared to Ortho-Cept
* means adjusted for effects of age.

Table 14. Range of non-bleeding intervals by reference period.*

Reference Period	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P¹	P²	P³
1	1.0 ± 0.2 (N = 101)	2.6 ± 0.2 (N = 95)	2.7 ± 0.2 (N = 90)	<.01	<.01	.95
2	1.1 ± 0.2 (N = 78)	2.7 ± 0.2 (N = 74)	2.7 ± 0.2 (N = 66)	<.01	<.01	.99
3	0.9 ± 0.3 (N = 62)	2.8 ± 0.3 (N = 66)	2.8 ± 0.3 (N = 59)	<.01	<.01	.99
4	0.6 ± 0.2 (N = 56)	2.8 ± 0.2 (N = 58)	2.8 ± 0.2 (N = 50)	<.01	<.01	.99
5	0.3 ± 0.2 (N = 47)	2.6 ± 0.2 (N = 61)	2.6 ± 0.2 (N = 43)	<.01	<.01	.99
6	0.2 ± 0.2 (N = 40)	2.5 ± 0.2 (N = 59)	2.6 ± 0.2 (N = 39)	<.01	<.01	.99
7	0.0 ± 0.2 (N = 22)	2.0 ± 0.2 (N = 25)	1.7 ± 0.3 (N = 19)	<.01	<.01	.57

P¹ = Depo compared to Ortho-Cept
P² = Depo compared to Ortho-Novum
P³ = Ortho-Novum compared to Ortho-Cept
* means adjusted for effects of age.

Table 16. Weight at baseline, 6, 12, 18, and 24 months by contraceptive method.*

	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P¹	P²	P³
Baseline	132.0 ± 3.4 (N = 101)	134.4 ± 3.2 (N = 94)	135.6 ± 3.5 (N = 90)	.99	.54	.99
6-months	134.5 ± 3.5 (N = 84)	136.2 ± 3.4 (N = 85)	137.1 ± 3.8 (N = 73)	.99	.99	.99
12-months	133.2 ± 4.3 (N = 63)	134.4 ± 4.1 (N = 69)	133.6 ± 4.4 (N = 65)	.99	.99	.99
18-months	136.4 ± 5.6 (N = 49)	137.5 ± 5.4 (N = 58)	134.4 ± 5.7 (N = 45)	.99	.99	.99
24-months	135.2 ± 4.8 (N = 45)	135.5 ± 4.5 (N = 59)	135.2 ± 4.9 (N = 42)	.99	.99	.99

P¹ = Depo compared to Ortho-Cept
P² = Depo compared to Ortho-Novum
P³ = Ortho-Novum compared to Ortho-Cept
* means adjusted for effects of age.

Table 17. Body mass index at baseline, 6, 12, 18, and 24 months by contraceptive method.*

	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P¹	P²	P³
Baseline	16.3 ± 10.9 (N = 101)	27.5 ± 10.4 (N = 95)	16.6 ± 11.5 (N = 90)	.61	.99	.65
6-months	22.6 ± 0.6 (N = 48)	22.7 ± 0.6 (N = 85)	23.1 ± 0.7 (N = 73)	.99	.99	.99
12-months	22.6 ± 0.8 (N = 63)	22.5 ± 0.8 (N = 69)	22.8 ± 0.8 (N = 65)	.99	.99	.99
18-months	23.1 ± 1.1 (N = 49)	22.7 ± 1.1 (N = 58)	22.9 ± 1.1 (N = 45)	.99	.99	.99
24-months	23.2 ± 1.0 (N = 45)	22.7 ± 0.9 (N = 59)	23.1 ± 1.0 (N = 42)	.99	.99	.99

P¹ = Depo compared to Ortho-Cept
P² = Depo compared to Ortho-Novum
P³ = Ortho-Novum compared to Ortho-Cept
* means adjusted for effects of age.

Table 18. Blood pressure at baseline, 6, 12, 18, and 24 months by contraceptive method.*

	Systolic Diastolic	Depo-Provera Mean Std Err	Ortho-Cept Mean Std Err	Ortho-Novum Mean Std Err	P[1]	P[2]	P[3]
Baseline		107.7 ± 2.0	109.6 ± 1.9	109.0 ± 2.1	.64	.99	.99
		66.5 ± 1.7 (N = 101)	65.8 ± 1.6 (N= 95)	65.2 ± 1.8 (N = 89)	.99	.99	.99
6-months		113.2 ± 2.0	116.7 ± 1.9	116.8 ± 2.1	.12	.11	.99
		65.1 ± 1.6 (N = 78)	67.3 ± 1.5 (N = 75)	65.4 ± 1.7 (N = 65)	.31	.99	.51
12-months		111.7 ± 2.5	113.7 ± 2.3	113.8 ± 2.6	.94	.85	.99
		64.3 ± 2.1 (N = 63)	64.4 ± 2.0 (N = 69)	63.6 ± 2.2 (N = 62)	.99	.99	.99
18-months		109.0 ± 3.0	111.1 ± 2.9	109.6 ± 3.1	.89	.99	.99
		63.4 ± 2.6 (N = 49)	65.2 ± 2.5 (N = 57)	61.1 ± 2.6 (N = 44)	.93	.55	.05
24-months		111.5 ± 3.3	110.5 ± 3.0	113.7 ±3.4	.99	.99	.73
		63.0 ± 2.2 (N = 45)	62.6 ± 2.0 (N = 58)	61.4 ± 2.3 (N = 41)	.99	.99	.99

P[1] = Depo compared to Ortho-Cept
P[2] = Depo compared to Ortho-Novum
P[3] = Ortho-Novum compared to Ortho-Cept
• means adjusted for effects of age.

Table 19. Side Effects.

Headaches	Ortho-Novum	Ortho-Cept	Depo-Provera	P
Baseline	43/95 (45.3%)	49/96 (51%)	42/103 (40.8%)	.35
6 months	21/53 (39.6%)	28/59 (47.5%)	21/61 (34.4%)	.34
12 months	24/43 (55.8%)	24/48 (50%)	18/54 (33.3%)	.07
18 months	Data error			
24 months	14/25 (56%)	19/30 (63.3%)	11/27 (40.7%)	.22

Nervous	Ortho-Novum	Ortho-Cept	Depo-Provera	P
Baseline	15/115 (13%)	9/127 (7.1%)	4/135 (3%)	.01
6 months	4/51 (7.8%)	8/57 (14%)	7/60 (11.7%)	.59
12 months	5/42 (11.9%)	7/45 (15.6%)	4/52 (7.7%)	.48
18 months	3/31 (9.7%)	4/37 (10.8%)	3/32 (9.4%)	.98
24 months	2/23 (8%)	0/29	1/26 (3.8%)	.30

Nausea	Ortho-Novum	Ortho-Cept	Depo-Provera	P
Baseline	12/115 (10.4%)	16/127 (12.6%)	17/135 (12.6%)	.84
6 months	10/50 (20%)	12/58 (20.7%)	9/62 (14.5%)	.63
12 months	10/42 (23.8%)	7/45 (15.6%)	5/52 (9.6%)	.17
18 months	3/31 (9.7%)	6/38 (15.8%)	1/31 (3.2%)	.22
24 months	2/25 (8%)	4/29 (13.9%)	0/26	.15

Dizzy	Ortho-Novum	Ortho-Cept	Depo-Provera	P
Baseline	11/96 (11.5%)	15/104 (14.4%)	17/118 (14.4%)	.78
6 months	5/50 (10%)	8/57 (14%)	10/62 (16.1%)	.64
12 months	9/43 (20.9%)	6/44 (13.6%)	6/52 (11.5%)	.42
18 months	5/31 (16.1%)	5/37 (13.5%)	5/31 (16.1%)	.94
24 months	1/25 (4%)	4/29 (13.8%)	4/26 (15.4%)	.38

Table 19 Side Effects (cont'd)

Breast Tenderness	Ortho-Novum	Ortho-Cept	Depo-Provera	P
Baseline	29/115 (25.2%)	53/127 (41.7%)	38/135 (28.1%)	.01
6 months	17/53 (32.1%)	30/59 (50.8%)	8/61 (13.1%)	<.01
12 months	16/44 (36.4%)	11/45 (24.4%)	11/52 (21.2%)	.22
18 months	11/31 (35.5%)	12/38 (31.6%)	5/32 (15.6%)	.17
24 months	7/25 (28%)	12/30 (40%)	3/27 (11.1%)	.05

Weight Gain	Ortho-Novum	Ortho-Cept	Depo-Provera	P
Baseline	22/115 (19.1%)	26/127 (20.5%)	25/135 (18.5%)	.92
6 months	17/51 (33.3%)	23/61 (37.7%)	36/62 (58.1%)	.02
12 months	16/44 (36.4%)	11/45 (24.4%)	11/52 (21.2%)	.22
18 months	11/31 (35.5%)	12/38 (31.6%)	5/32 (15.6%)	.17
24 months	9/25 (36%)	9/29 (31%)	12/26 (46.2%)	.50

Table 20. Dysmenorrhea

Dysmenorrhea (moderate or severe)	Ortho-Novum	Ortho-Cept	Depo-Provera	P
Baseline	31/89 (34.8%)	33/94 (35.1%)	33/99 (33.3%)	.96
6 months	10/76 (13.2%)	14/84 (16.7%)	9/79 (11.4%)	.61
12 months	11/65 (16.9%)	10/69 (14.5%)	6/53 (11.3%)	.69
18 months	6/48 (12.5%)	3/60 (5%)	2/38 (5.3%)	.28
24 months	3/40 (7.5%)	5/59 (8.5%)	2/33 (6.1%)	.92

Days pain lasts (2 or more)	Ortho-Novum	Ortho-Cept	Depo-Provera	P
Baseline	36/88 (40.9%)	44/94 (46.8%)	38/100 (38%)	.45
6 months	24/75 (32%)	36/84 (42.9%)	17/81 (21%)	.01
12 months	21/64 (32.8%)	21/68 (30.9%)	8/57 (14%)	.04
18 months	18/48 (37.5%)	15/60 (25%)	4/40 (10%)	.01
24 months	11/40 (27.5%)	19/58 (32.8%)	0/37	<.01

Table 21. Frequency of headaches.

Frequency of headaches (1 or more per week)	Ortho-Novum	Ortho-Cept	Depo-Provera	P
Baseline	17/87 (19.5%)	15/93 (16.1%)	15/100 (15%)	.69
6 months	16/74 (21.6%)	17/85 (20%)	16/88 (18.2%)	.86
12 months	10/61 (16.4%)	12/66 (18.2%)	11/63 (17.5%)	.97
18 months	11/47 (23.4%)	9/60 (15%)	9/49 (18.4%)	.54
24 months	7/42 (16.7%)	8/59 (13.6%)	7/45 (15.6%)	.91

Table 22. Total number of spotting days for Depo users.

Reference Period	0-7 days	8-15 days	16-22 days	23-29 days	>29 days
1	82/101 (81.2%)	8/101 (7.9%)	1/101 (1%)	3/101 (3%)	7/101 (6.9%)
2	58/78 (74.4%)	10/78 (12.8%)	4/78 (5.1%)	2/78 (2.6%)	4/78 (5.1%)
3	54/62 (87.1%)	4/62 (6.5%)	2/62 (3.2%)		2/62 (3.2%)
4	53/56 (94.6%)	3/56 (5.4%)			
5	47/47 (100%)				
6	38/40 (95%)	2/40 (5%)			
7	22/22 (100%)				

Table 23. Total number of bleeding/spotting days for Depo users.

Reference Period	0-7 days	8-15 days	16-22 days	23-29 days	>29 days
1	43/101 (42.6%)	15/101 (14.9%)	7/101 (6.9%)	2/101 (2%)	34/101 (33.7%)
2	46/78 (59%)	9/78 (11.5%)	9/78 (11.5%)	3/78 (3.8%)	11/78 (14.1%)
3	50/62 (80.6%)	2/62 (3.2%)	1/62 (1.6%)	2/62 (3.2%)	7/62 (11.3%)
4	42/56 (75%)	6/56 (10.7%)	4/56 (7.1%)	2/56 (3.6%)	2/56 (3.6%)
5	43/47 (91.5%)	2/47 (4.3%)		1/47 (2.1%)	1/47 (2.1%)
6	38/40 (95%)		1/40 (2.5%)		1/40 (2.5%)
7	22/22 (100%)				

Table 24. Days to first bleed for Depo subjects.

	N	Minimum	Maximum	Mode	Median	Mean	Std. Deviation
Days to first bleed	100	0	85	0	0	8.21	15.06

(0 excluded)	N	Minimum	Maximum	Mode	Median	Mean	Std. Deviation
Days to first bleed	39	1	85	1,4,23	17	21.05	17.71

(85 excluded)	N	Minimum	Maximum	Mode	Median	Mean	Std. Deviation
Days to first bleed	99	0	53	0	0	7.43	12.98

(0, 85 excluded)	N	Minimum	Maximum	Mode	Median	Mean	Std. Deviation
Days to first bleed	38	1	53	1,14,23	15.5	19.37	14.45

Table 25. Within group comparisons for total # of bleeding/spotting days for those who discontinued vs. those who continued.

Reference Period	Depo-Provera Mean Std Err	P	Ortho-Cept Mean Std Err	P	Ortho-Novum Mean Std Err	P
Ref. 1 v 2	19.1 ± 5.1 37.8 ± 8.0 (N = 78,23)	.02	16.6 ± 1.3 15.8 ± 1.6 (N = 74,21)	.62	16.7 ± 1.4 16.4 ± 1.8 (N = 66,24)	.88
Ref. 1 v 2 1162 excluded	18.4 ± 4.2 29.5 ± 6.7 (N = 78,22)	.10				
Ref. 1 v 3	17.8 ± 5.7 30.7 ± 6.5 (N = 62,39)	.08	16.8 ± 1.3 15.5 ± 1.4 (N = 66,29)	.33	17.1 ± 1.4 15.3 ± 1.7 (N = 59,31)	.27
Ref. 1 v 3 1162 excluded	17.6 ± 4.7 25.3 ± 5.4 (N = 62,38)	.20				
Ref 1 v 4	17.6 ± 5.8 29.7 ± 6.3 (N = 56,45)	.09	16.8 ± 1.3 15.7 ± 1.3 (N = 58,37)	.33	16.7 ± 1.5 16.4 ± 1.6 (N = 50,40)	.81
Ref. 1 v 4 1162 excluded	17.5 ± 4.8 24.7 ± 5.2 (N = 56,44)	.22				
Ref 2 v 3	8.5 ± 3.0 18.7 ± 4.7 (N = 61,15)	.05				
Ref 3 v 4	7.3 ± 6.2 6.9 ± 2.7 (N = 56,6)	.95				

- means adjusted for effects of age.

Table 26. Within group comparisons for total # of spotting days for those who discontinued vs. those who continued.

Reference Period	Depo-Provera Mean Std Err	P	Ortho-Cept Mean Std Err	P	Ortho-Novum Mean Std Err	P
Ref. 1 v 2	11.1 ± 3.0 13.5 ± 4.6 (N = 78,23)	.61	0.1 ± 0.2 0.0 ± 0.2 (N = 74,21)	.62	0.3 ± 0.7 0.3 ± 1.0 (N = 66,24)	.95
Ref. 1 v 3	9.9 ± 3.2 14.2 ± 3.7 (N = 62,39)	.30	0.0 ± 0.2 0.2 ± 0.2 (N = 66,29)	.14	0.0 ± 0.7 1.5 ± 0.9 (N = 59,31)	.06
Ref 1 v 4	9.4 ± 3.3 14.3 ± 3.5 (N = 56,45)	.22	0.0 ± 0.2 0.1 ± 0.2 (N = 58,37)	.32	0.0 ± 0.8 0.9 ± 0.8 (N = 50,40)	.24
Ref 2 v 3	5.7 ± 2.7 8.1 ± 4.2 (N = 61,15)	.61				
Ref 2 v 4	2.2 ± 1.5 8.8 ± 3.3 (N = 56,6)	.05				

Table 27. Frequency of dizzy spells.

Frequency of dizzy spells (1 or more per week)	Ortho-Novum	Ortho-Cept	Depo-Provera	P
Baseline	1/87 (1.1%)	2/93 (2.2%)	3/98 (3.1%)	.67
6 months	5/74 (6.8%)	2/84 (2.4%)	3/86 (3.5%)	.36
12 months			3/63 (4.8%)	.05
18 months	1/47 (2.1%)		3/49 (6.1%)	.13
24 months			1/45 (2.2%)	.32

Table 28. Comparison of differences in weight.

	Depo-Provera Mean Std dev	P	Ortho-Cept Mean Std dev	P	Ortho-Novum Mean Std dev	P
B-6	134.42 ± 18.97 135.49 ± 18.43 (N = 84)	.21	136.08 ± 18.11 136.65 ± 17.96 (N = 84)	.31	136.81 ± 18.05 138.18 ± 18.29 (N = 73)	.07
B-12	134.79 ± 18.96 137.52 ± 18.76 (N = 63)	.05	137.88 ± 18.56 137.81 ± 18.63 (N = 68)	.94	135.45 ± 18.08 137.83 ± 19.01 (N = 65)	.05
B-18	135.51 ± 19.20 139.57 ± 20.49 (N = 49)	.05	139.41 ± 17.83 139.83 ± 17.95 (N = 58)	.72	135.02 ± 17.22 137.93 ± 17.36 (N = 45)	.02
B-24	135.67 ± 18.59 141.69 ± 19.72 (N = 45)	<.01	139.34 ± 18.18 140.66 ± 17.89 (N = 58)	.33	136.26 ± 20.08 141.07 ± 21.37 (N = 42)	<.01
6-12	135.90 ± 18.13 137.76 ± 18.82 (N = 62)	.04	137.88 ± 18.37 137.67 ± 18.53 (N = 69)	.77	137.26 ± 18.12 138.21 ± 19.50 (N = 61)	.29
12-18	137.53 ± 18.90 139.57 ± 20.49 (N = 49)	.03	139.17 ± 17.55 139.83 ± 17.95 (N = 58)	.29	137.38 ± 17.66 137.93 ± 17.36 (N = 45)	.45
18-24	140.39 ± 20.47 141.50 ± 19.91 (N = 44)	.33	140.83 ± 18.03 140.72 ± 17.96 (N = 58)	.89	138.36 ± 18.25 139.19 ± 19.35 (N = 36)	.46

Paired samples T test

Table 28. Comparison of differences in weight.

	Depo-Provera Mean Std dev	P	Ortho-Cept Mean Std dev	P	Ortho-Novum Mean Std dev	P
B-6	134.42 ± 18.97 135.49 ± 18.43 (N = 84)	.21	136.08 ± 18.11 136.65 ± 17.96 (N = 84)	.31	136.81 ± 18.05 138.18 ± 18.29 (N = 73)	.07
B-12	134.79 ± 18.96 137.52 ± 18.76 (N = 63)	.05	137.88 ± 18.56 137.81 ± 18.63 (N = 68) **(*3)**	.94	135.45 ± 18.08 137.83 ± 19.01 (N = 65)	.05
B-18	135.51 ± 19.20 139.57 ± 20.49 (N = 49)	.05	139.41 ± 17.83 139.83 ± 17.95 (N = 58)	.72	135.02 ± 17.22 137.93 ± 17.36 (N = 45)	.02
B-24	135.67 ± 18.59 141.69 ± 19.72 (N = 45)	<.01	139.34 ± 18.18 140.66 ± 17.89 (N = 58)	.33	136.26 ± 20.08 141.07 ± 21.37 (N = 42)	<.01
6-12	135.90 ± 18.13 137.76 ± 18.82 (N = 62) **(*1)**	.04	137.88 ± 18.37 137.67 ± 18.53 (N = 69)	.77	137.26 ± 18.12 138.21 ± 19.50 (N = 61) **(*4)**	.29
12-18	137.53 ± 18.90 139.57 ± 20.49 (N = 49)	.03	139.17 ± 17.55 139.83 ± 17.95 (N = 58)	.29	137.38 ± 17.66 137.93 ± 17.36 (N = 45)	.45
18-24	140.39 ± 20.47 141.50 ± 19.91 (N = 44) **(*2)**	.33	140.83 ± 18.03 140.72 ± 17.96 (N = 58)	.89	138.36 ± 18.25 139.19 ± 19.35 (N = 36) **(*5)**	.46

Paired samples T test

1. #207 no weight at 6 mo for Depo
2. #1210 no weight at 18 mo for Depo (discontinued at 18 but has weight for 24)
3. #36 weight not taken at baseline for Ortho-Cept
4. #90, #93, #120, #1064 have no weight at 6 mo but have weight at 12 mo for Ortho-Novum
5. #43, #142, #144, #1011, #1015, #1062 no weight at 18 mo for Ortho-Novum
   *#142, #1011, #1062 all are discontinued at 18 mo but have weight at 24mo

DEPARTMENT OF THE ARMY
US ARMY MEDICAL RESEARCH AND MATERIEL COMMAND
504 SCOTT STREET
FORT DETRICK, MARYLAND 21702-5012

REPLY TO
ATTENTION OF:

MCMR-RMI-S (70-1y) 1 Apr 03

MEMORANDUM FOR Administrator, Defense Technical Information Center (DTIC-OCA), 8725 John J. Kingman Road, Fort Belvoir, VA 22060-6218

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Materiel Command has reexamined the need for the limitation assigned to technical reports written for this Command. Request the limited distribution statement for the enclosed accession document numbers be changed to "Approved for public release; distribution unlimited." Copies of these reports should be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Judy Pawlus at DSN 343-7322 or by e-mail at judy.pawlus@det.amedd.army.mil.

FOR THE COMMANDER:

Encl

PHYLLIS M. RINEHART
Deputy Chief of Staff for
Information Management

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